REMARKS

Applicant respectfully requests reconsideration. Claims 1-11, 14, 17 and 22-24 were previously pending in this application. Claims 1, 3-10, 14, 17 and 23 have been amended. The claim amendments have been made for clarification purposes. Support for the claims amendments can be found, for example, in the claims as originally filed and in the specification on pages 4-5. Claim 11 has been canceled. As a result, claims 1-10, 14, 17 and 22-24 are pending for examination with claim 1 being an independent claim. No new matter has been added.

Objection to the Specification

The Examiner has indicated that the listing of references in the specification is not a proper information disclosure statement. The Examiner has further stated that removal of the listing from the specification and submission via a Form PTO-892 for consideration would be remedial.

Applicant respectfully traverses this objection. The listing of references in the specification is not intended by Applicant to be a proper information disclosure statement. Applicant has submitted references as appropriate and in satisfaction of 35 C.F.R. §1.56 and in compliance with 35 C.F.R. §1.97 and 1.98. In addition, Applicant notes that the listing of references in the specification as currently presented is allowed under 35 C.F.R. §1.57 and, therefore, its removal is not required.

Accordingly, Applicant respectfully requests that this objection be withdrawn.

Double Patenting Rejection

The Examiner has provisionally rejected claims 1-4, 6-11, 14, 17 and 22-24 on the ground of non-statutory obviousness-type double patenting as being allegedly unpatentable over claims 1-21 and 23-25 of co-pending application (U.S. Serial No. 11/081945).

The Examiner has raised a *provisional* double patenting rejection based on a co-pending unallowed application. In view of the unallowed state of the co-pending application, Applicant proposes that this issue be at present deferred and maintains the right to subsequently address this rejection.

Enablement Rejections under 35 U.S.C. §112

The Examiner rejected claims 1-11, 14, 17 and 22-24 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. According to the Examiner, the steps of transfecting a cell line with a construct encoding a desired gene and selecting cell lines that have integrated the transgene into its genome are not enabled in themselves. In addition, the Examiner argues that at present the state of the art is that transgenic animals cannot be produced by transfecting cells.

Applicant respectfully traverses. According to MPEP §2164.04, in order to make an enablement rejection, the examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). Applicant maintains that the Examiner has failed to satisfy this burden. The Examiner has referred to various references and has asserted various arguments, all of which do not provide a reasonable basis to question the enablement provided by the instant disclosure as discussed further below.

Firstly, the Examiner refers to Zakhartchenko et al. to support her argument that transgenic animals cannot be produced by transfecting cells. Applicant notes that this reference predate the filing of instant invention by four years. A subsequent reference closer in date to the filing of instant application rebuts Zakhartchenko et al. Bordignon et al. (Bordignon et al., 2003 Biol Reprod, 68: 2013-2023) teaches that "*In vitro* transfection of cultured cells combined with nuclear transfer currently is the most effective procedure to produce transgenic livestock." (First line of the abstract; reference was also referred to on page 10 of the Office Communication). Bordignon et al. also present a method relating to transfecting fibroblast cells with a GFP reporter gene, nuclear transfer and the generation of calves expressing GFP in all tissues examined. The state of the art, therefore, at the time of filing of the current application provides that the generation of transgenic animals through nuclear transfer of transfected cells could be produced contrary to the Examiner's assertion.

The Examiner further states that "the resulting phenotype would not be predictable" and that "the unpredictability lies with the site of integration of the transgene into the target genome." [page 7]. The examiner proceeds by referring to a number of publications, most of which predate the current application by five years or more. However, the publications referred to by the Examiner also make it clear that, while there may be variations in efficiency, there is no fundamental reason that would prevent transgenic animals from being generated. As the claims of the current invention do not require any particular efficiency, there are no enablement issues. In addition, the specification offers written support for screening methods [50], including Southern blotting and PCR, which allow for the identification of a successful transfection and nuclear transfer event. No undue experimentation is therefore required to enable the claimed invention.

According to the Examiner, nuclear transfer is an unpredictable art. The specification provides general guidelines for nuclear transfer and some specifics as they pertain to goats, yet the breath of the claim is to all animals [page 9]. The Examiner further refers to Westhusin et al. (2001 Theriogenology 55: 35-40). The authors of this publication state when referring to nuclear transfer, that "these techniques and the efficiency of these techniques varies from species to species." However, the claimed invention clearly enables nuclear transfer. Support for the enablement of nuclear transfer pertaining to any animal is provided in the written description in [35-37], and written description support pertaining to goats in particular is provided in [46-47]. Again, while there may be small differences in nuclear transfer techniques and efficiencies between species, a person of ordinary skill in the art would be able to perform nuclear transfer in any animal based on the written description provided in the specification and readily available materials in the prior art.

According to the Examiner increased unpredictability occurs when combining transgenic techniques with nuclear transfer [page 10]. One of the publications the Examiner refers to is Bordignon et al. (2003 Biol Reprod, 68: 2013-2023). Bordignon et al. teach that the expression levels of the transgenic gene varies between tissues and even within tissues. However, the Bordignon reference also offers an example of the ability to generate a transgenic animal through nuclear transfer of transfected cells. The animals are transgenic as the introduced gene is found in all tissues. The animal is still transgenic even if the gene does not express at the same level in

every tissue. 'High expression levels in every tissue' is not claimed in the current invention. What is claimed is the generation of a transgenic animal, and those claims are enabled.

The Examiner objected to the phrase 'selecting cells homozygous for the transgene using a selective agent and characterizing surviving cells' because nothing links the steps of producing the transgenic cell line and first transgenic animal to these steps [page 10]. Applicant has addressed the objection by amending the claim to recite: "obtaining cells from said first heterozygous transgenic animal and selecting cells homozygous for the desired transgene through the use of a selective agent".

The Examiner objected to the use of the word 'cell' in this part of the claim, when earlier parts of the claim were drawn to 'cell lines' [page 11]. Applicant has amended the claim to resolve the 'lack of clarity'. The first part of the method pertains to the transfection, which can be performed with cell lines (e.g. established cell lines) or cells (e.g. cells obtained from an animal, but not established as a cell line). The first part of the claim has been amended and now recites: "transfecting a non-human mammalian cell or cell-line with a given transgene construct containing at least one DNA encoding a desired gene; selecting a cell or cell line~~(s)~~ in which the desired gene has been inserted into the genome of that cell or cell-line". The second part of the method pertains to cells harvested from an heterozygous animal, which are subsequently subjected to an agent, selected for, and used for a second round of nuclear transfer. It would therefore be confusing to replace 'cells' with 'cell lines' in the second part of the claim. However to clarify the claim, Applicant has amended to claim to recite: "characterizing surviving cells or cell colonies ~~using known molecular biology methods~~; ~~and~~ picking surviving cells or cell colonies ~~cells~~ for use in a second round of nuclear transfer or embryo transfer".

Furthermore, the Examiner objected to the claims because 'elevated do(s)es of a selective agent to select for the homozygote' is not represented in the claims [page 11. Applicant has addressed the objection by the Examiner and amended the claims to recite: "selecting cells homozygous for the desired transgene through the use of a selective agent, whereby the dose of the selective agent is increased to select for homozygous cells". Support for this claim recitation be found in the specification at least in [25] and Example 1.

Furthermore, according to the Examiner, 'the selecting of cells or cell lines for transgene integration alone has been shown to be unpredictable'. The Examiner refers to a publication by Chen et al. (2002, Biol Reprod 67: 1488), who discuss the so-called' bystander effect', where

cells that have not taken up the transgene may be selected for. The objection of unpredictability raised by the Examiner falls within the realm of unpredictability of standard laboratory practices. The pitfalls connected to screening methods, including false positives, are known to one of ordinary skill in the art and do not preclude enablement of the claimed invention. One of ordinary skill in the art will know how to identify 'false positives' that may arise due to the 'bystander effect'. One easy test to confirm integration of the transgene is a PCR assay, which is described in the specification in [50].

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Indefiniteness Rejections under 35 U.S.C. §112

The Examiner has objected to the limitation 'said donor' for not having sufficient antecedent basis. Applicant has amended claims 1 and 6-8 to clarify what is intended by donor cell or cell nucleus. Accordingly, Applicant believes this rejection is now moot.

The Examiner has rejected claims 1-11, 14, 17 and 22-24 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner has objected to the term "several known molecular biology methods" for being vague and indefinite. Applicant has amended claim 1 and 4 to remove the phrase "known molecular biology methods" and "several known molecular biology methods", respectively. Accordingly, Applicant believes this rejection is now moot.

The Examiner has objected to the recitation "without limitation FISH". Applicant has amended claim 4 to simplify the language in the claim. Accordingly, Applicant believes this rejection is now moot.

Rejections over WO 00/42174 under 35 U.S.C. §102

The Examiner has rejected claims 1, 4-11, 14, 17 and 22-24 under 35 U.S.C. §102(b) as allegedly being anticipated by WO 00/42174. According to the Examiner, WO 00/42174 discloses the production of transgenic or non-transgenic animals by two consecutive rounds of nuclear transfer. The Examiner further indicates that due to the breadth of the disclosure of WO 00/42174, the narrower scope of transfecting a transgene into a cell, selecting a cell containing a transgene and doing rounds of nuclear transfer to produce a first transgenic heterozygous offspring that is homozygous and/or heterozygous for the transgene is encompassed by the

disclosure. The Examiner also alleges that various dependent limitations are also found in WO 00/42174.

Applicant respectfully traverses. Firstly, the teachings of WO 00/42172 do not provide a positive teaching of Applicant's claimed methods. The Examiner argues that WO 00/42172 discloses a production process for transgenic animals combining transfection, selection and nuclear transfer in any combination and that such a broad teaching encompasses a method of narrower scope. Even if, *arguendo*, the Examiner is correct that WO 00/42172 provides a broad teaching of a method that encompasses within its scope Applicant's claimed methods, without a positive teaching of Applicant's claimed methods, WO 00/42172 is not anticipatory. The Examiner is respectfully reminded that the teaching of a genus does not necessarily anticipate claims to species within that genus. See, e.g., MPEP §2131.02.

Secondly, according to MPEP §2131, in order for a reference to be anticipatory it must teach every element of the claim. The claimed invention discloses a method which includes a number of limitations, such as transfecting a cell or cell line with a transgene, performing a nuclear transfer using this transgenic cell or cell line, obtaining a heterozygous animal, selecting for cell(s) that are homozygous, performing a second nuclear transfer and obtaining a homozygous transgenic animal. In the passages of WO 00/42174 to which the Examiner refers all of the limitations of Applicant's claims cannot be found. If the Examiner maintains the rejection, the Examiner is respectfully requested to indicate where each and every limitation of Applicant's claims are recited in WO 00/42174 (See MPEP §§ 706.02 (j), 707).

Finally, in order for a reference to be anticipatory it must also be enabling (See MPEP §2121). On page 16 of the Office Communication, the Examiner admits that the teachings of WO 00/42172 are not enabling. Therefore, on at least this basis alone, the Examiner's rejection cannot be maintained.

Accordingly, for the reasons provided above, withdrawal of this rejection is respectfully requested.

Rejections over US2002/0069423 under 35 U.S.C. §102

The Examiner has rejected claims 1, 4-11 and 22-24 under 35 U.S.C. §102(e) as being anticipated by US2002/0069423. According to the Examiner, US2002/0069423 discloses the production of a transgenic cow that has a deletion in the PRNP gene. Further, according to the Examiner, US2002/0069324 discloses all the elements of the current claimed invention.

Applicant respectfully traverses. Applicant maintains that the methods provided by US 2002/006942 are different from Applicant's claimed methods. US 2002/0069423 describes three ways to generate homozygous animals (See, e.g., paragraph 46, last two sentences). The three ways are obtaining homozygous transgenic ungulates 1) by breeding the heterogeneous transgenic ungulates, 2) by targeting a deletion of the other allele using primary fibroblasts, or 3) by a homozygous deletion or disruption isolated in the initial fibroblast cell. The currently claimed invention, however, provides a different method of generating a homozygous animal, namely performing a first round of nuclear transfer, selecting for cells that are homozygous and performing a second round of nuclear transfer. As the methods provided in the reference cited by the Examiner are different from Applicant's claimed methods, the claimed methods are not anticipated by US 2002/0069423.

Applicant respectfully submits that the statement in paragraph 172 of US 2002/0069423, which recites "Previous work on bovine somatic cell nuclear transfer has demonstrated that this technique is *repeatable* not only with primary cells from fetuses and adult animals but with transgenic cells as well", has been misinterpreted. This statement means that somatic cell transfer can be done with both primary cells and with transgenic cells. The statement does not refer to 'repeated rounds of nuclear transfer'.

Furthermore, as described above, in order for a reference to be anticipatory it must also be enabling (See MPEP §2121). On page 19 of the Office Communication, the Examiner admits that the teachings of US 2002/006942 are not enabling. Again, for at least this reason alone, the Examiner's rejection of Applicant's claims cannot be maintained.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections over US 5,945,577 under 35 U.S.C. §102

The Examiner has rejected claims 1-11, 14, 17 and 22-24 under 35 U.S.C. §102(b) as being anticipated by US 5,945,577. According to the Examiner, US 5,945,577 discloses the use

of ungulate inner cell mass for nuclear transplantation and asserts that it would have been obvious to an artisan that this technique could be repeated in multiple rounds.

Applicant respectfully traverses. The Examiner has not met the Patent Office's burden of establishing a proper basis for asserting an anticipation rejection and merely argues that the reference discloses nuclear transplantation and that it would have been obvious that this technique could be repeated. What would now - after reading Applicant's specification - be obvious is not the basis for asserting a rejection under 35 U.S.C. §102 and as such the Examiner's arguments are not sufficient to assert that US 5,945,577 anticipates Applicant's claimed methods. Moreover, in the absence of any support, such a mere assertion could not support an obviousness rejection either.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections over US 5,633,076 under 35 U.S.C. §102

The Examiner has rejected claims 1-11, 14, 17 and 22-24 under 35 U.S.C. §102(b) as being anticipated by US 5,633,076. According to the Examiner US 5,633,076 discloses that transgenic cows were produced from blastocytes that were analyzed prior to nuclear transfer and that it would be obvious to an artisan that this could be repeated multiple rounds.

Applicant respectfully traverses. The arguments presented by the Examiner are not sufficient to assert an anticipation rejection. What would be obvious to the ordinarily skilled artisan is irrelevant for establishing anticipation. Again, such an unsupported assertion would also be insufficient for an obviousness rejection.

Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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